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A MILD AND VARIABLE SYNTHESIS OF α-KETOESTERS

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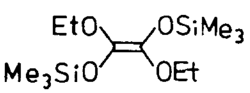
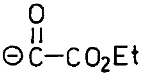
Summary: The $ZnCl_2$ promoted addition of 1,2-diethoxy-1,2-disilyloxyethylene 1 with electrophiles such as aldehydes, ketones, α,ß-unsaturated ketones or tertiary alkyl halides allows for a simple synthesis of α-ketoesters.

α-Ketoesters and acids not only represent useful compounds in organic synthesis, e.g., in the construction of heterocycles 1), but also play an important role in various biological processes 2). A number of rational syntheses have been designed 2,3,4). This communication describes a novel entry into α-ketoesters having additional functionality.

We have discovered that compound 1 (prepared by reacting oxalic acid ester with Na/K and trimethylsilyl chloride) 5) reacts with carbonyl compounds in the presence of catalytic amounts of Lewis acids (e.g., $ZnCl_2$) or bases ($F^{\ominus}$) to form aldol or Michael addition products 6). This means that 1 can be viewed as a synthon 3) for the anion 1'.

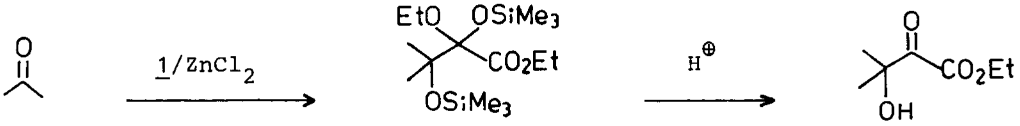


1



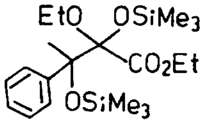
1'

For example, the reaction of 1 with one equivalent of acetone 2 in the presence of catalytic amounts of $ZnCl_2$ in dry CH_2Cl_2 at room temperature (3 h) results in essentially quantitative formation of 3 (87% isolated after stripping off solvent and distilling at 80 °C/0.1 torr). 3 is the protected form of 4, which can be obtained directly from the crude product by stripping off the solvent and treating with CH_3OH/2 N HCl (40:1) at room temperature (83% isolated by filtering over a short SiO_2 column/CH_2Cl_2)7) :

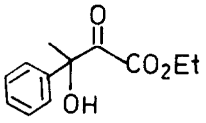


2 3 4

Similarly, compounds 5 (diastereomer ratio 2:1) and 6 were obtained using acetophenone:

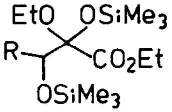


5 (80%)



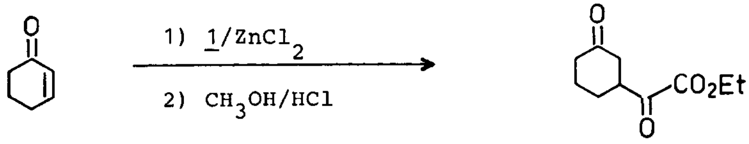
6 (75%)

The $ZnCl_2$ mediated reaction of 1 with aldehydes is extremely fast at room temparature (>90% conversion within 30-60 min). 7 and 8 were obtained in analytically pure form as 1:1 diastereomers by kugelrohr distillation7,8). They are the protected form of reductones 9).

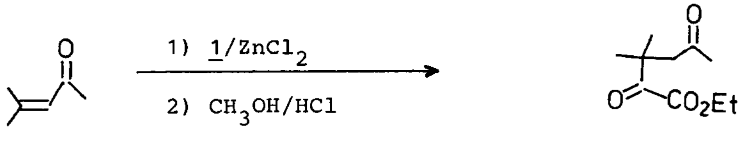


7 : R = phenyl (74%)
8 : R = ethyl (82%)

α,ß-Unsaturated ketones react smoothly at room temperature solely in a 1,4 manner (Michael addition), as exemplified by the simple synthesis of 10 and 12 7).

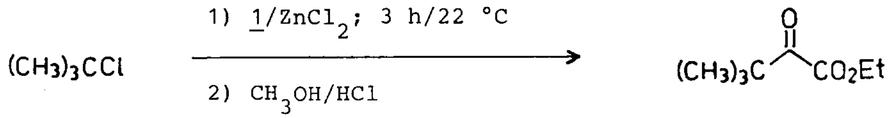


9 10 (84%)



11 12 (68%)

Finally, Lewis acid induced α-alkylation using S_N1 active alkyl halides[10] also occurs under mild conditions:



11 **12** (59%)

Physical and spectroscopic data of several compounds are given in footnotes[7,11]. *In summary, the present synthetic method makes α-ketoesters accessible which are not easily prepared by previous means*. Some of the compounds are likely to be useful starting materials for the synthesis of *heterocycles* and *α,β-unsaturated α-amino acids*.

Acknowledgement: This work was supported by the Fonds der Chemischen Industrie.

Footnotes:

1) See for example: E.J. Corey, H.S. Sachdev, T.Z. Gougoutas and W. Saenger, *J. Am. Chem. Soc*. **92**, 2488 (1970).

2) Recent findings: C. Klein, G. Schulz and W. Steglich, *Liebigs Ann. Chem*. **1983**, 1623 and references cited therein; general discussion: A.L. Lehninger, *Biochemistry*, Worth, Chapter 21, N.Y. 1975; concerning the synthesis and biological importance of structurally related α,β-unsaturated α-amino acids see: H. Poisel and U. Schmidt, *Angew. Chem*. **88**, 95 (1976); *Angew. Chem., Int. Ed. Engl*., **15**, 294 (1976); E. Gross and J.L. Morell, *J. Am. Chem. Soc*. **93**, 4634 (1971).

3) Use of dithianes as synthons for **1'**:E.L. Eliel and A.A. Hartman, *J. Org. Chem*. **37**, 505 (1972); M.L. Lissel, *Synth. Commun*. **11**, 343 (1981).

4) Recent reports: P. Müller and J. Godoy, *Tetrahedron Lett*. **1982**, 3661; E.D. Thorsett, *Tetrahedron Lett*. **1982**, 1875; J.S. Nimitz and H.S. Mosher, *J. Org. Chem*. **46**, 211 (1981); G.P. Axiotis, *Tetrahedron Lett*. **1981**, 1509; L.M. Weinstock, R.B. Currie and A.V. Lovell, *Synth. Commun*. **11**, 943 (1981); P.A. Manis and M.W. Rathke, *J. Org. Chem*. **45**, 4952 (1980); K. Ogura, N. Katoh, I. Yoshimura and G. Tsuchihashi, *Tetrahedron Lett*. **1978**, 375; and references in these articles.

5) Y.N. Kuo, F. Chen, C. Ainsworth and J.J. Bloomfield, *J. Chem. Soc., Chem. Commun*. **1971**, 136; in our hands the yield of distilled **1** based on oxalic acid ester was ∿25%. The substance is easy to handle and can be stored for months at room temperature. It is a Z/E mixture.

6) Silyl enol ethers derived from ketones or esters undergo aldol or Michael addition in the presence of such Lewis acids as $TiCl_4$: T. Mukaiyama, Angew. Chem. 89, 858 (1977); Angew. Chem., Int. Ed. Engl. 16, 817 (1977).

7) Typical procedure: Synthesis of 10: In a 100 ml round bottom flask with N_2-inlet 100 mg dry $ZnCl_2$ is heated under vacuum with a bunsen burner until the substance melts. After cooling to room temperature 20 ml of dry CH_2Cl_2, 10 mmol of 1 and 10 mmol of 9 are added and the mixture stirred for 45 min. under N_2. The solvent is stripped off and the crude product is treated with 20 ml CH_3OH containing 0,5 ml of 2 N HCl at room temperature for about 5 min. The solvent is stripped off and the product is passed through a short silica gel filter to provide 1.67 g (84%) of analytically pure 10: ^{1}H-NMR ($CDCl_3$): δ = 1.4 (t, 3H), 1.5-2.7 (m, 9H), 4.3 (q, 2H).

8) This as well as some of the other reactions can also be induced by $F^\ominus$ ions.

9) G. Hesse, Methoden der Organischen Chemie, Houben-Weyl-Müller, Vol. 6/1d, p. 217 ff (1978).

10) Review of Lewis acid promoted α-alkylation of carbonyl compounds using S_N1 active alkylation agents: M.T. Reetz, Angew. Chem. 94, 97 (1982); Angew. Chem., Int. Ed. Engl. 21, 96 (1982); see also P. Brownbridge, Synthesis 1983, 25; P. Brownbridge, Synthesis 1983, 285.

11) Compound 3 : Kugelrohr distillation (80°C/0.1 torr); ^{1}H-NMR ($CDCl_3$: δ = 0.13 (s, 9H), 0.22 (s, 9H), 1.13-1.55 (m, 12H), 3.05-3.77 (m, 2H), 4.2 (q, 2H); IR (film): 1745 cm^{-1}. Compound 4 (W.W.Wisaksono and J.F.Arens, Rec.Trav.Chim.Pays-Bas 80, 846 (1961)): ^{1}H-NMR ($CDCl_3$): δ = 1.30 (t, 3H), 1.42 (s, 6H), 3.53 (s, 1H), 4.37 (q, 2H). Compound 5 : ^{1}H-NMR ($CDCl_3$) : (diastereomer mixture) : δ = 0.04, 0.13, 0.16, 1.10, 1.20, 1.37, 1.77, 1.87, 3.0-3.8, 3.87-4.53, 7.03-7.77; IR(film): 1745 cm^{-1}; the compound was purified by kugelrohr distillation at 150°C/0.1 torr. Compound 6 : after treatment with CH_3OH/HCl[7], residue was filtered over a short silica gel filter using methylene chloride; ^{1}H-NMR ($CDCl_3$) δ = 1.12 (t, 3H), 1.70(s, 3H), 4.07 (q, 2H), 4.13 (s, 1H), 7.08-7.60 (m, 5H); IR(film): 1710 cm^{-1}. Compound 7 isolated by kugelrohr distillation at 100°C/0.1 torr (mixture of diastereomers) ^{1}H-NMR ($CDCl_3$) : δ = 0.05, 0.13, 0.93-1.63, 3.17-4.53, 4.93, 7.3; IR(film) : 1745 cm^{-1}. Compound 8 isolated by kugelrohr distillation at 95-100°C/ 0.1 torr (mixture of diastereomers); ^{1}H-NMR ($CDCl_3$) : δ = 0.01, 0.03, 0.06, 0.08, 0.90-1.50, 2.90-4.57; IR (film): 1750 cm^{-1}.

All of the compounds described in this communication gave correct elemental analyses.